UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/813,467	03/29/2004	Bill J. Peck	10031551-1	4799

22878 7590 12/06/2006

AGILENT TECHNOLOGIES INC.
INTELLECTUAL PROPERTY ADMINISTRATION, M/S DU404
P.O. BOX 7599
LOVELAND, CO 80537-0599

EXAMINER	
CROW, ROBERT THOMAS	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/813,467	PECK ET AL.
	Examiner	Art Unit
	Robert T. Crow	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 25 September 2006.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 28-59 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 28-59 is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. This action is in response to papers filed 25 September 2006 in which claims 28, 35-36, 56 were amended, no claims were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 112, second paragraph, not reiterated below are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections.

The previous rejections under the judicially created doctrine of obviousness-type double patenting not reiterated below are withdrawn in view of Applicant's arguments.

Claims 28-59 are under prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 36 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is indefinite in the recitation "at least about" in line 3 of the claim. The phrase "at least" typically indicates a minimum point; however, the phrase "at least" is controverted by the term "about," which implies that values above and below the indicated amount are permitted. Therefore, the juxtaposition of these two terms makes it unclear what minimum amount is encompassed by the claim. In

Amgen, Inc. v. Chugai Pharmaceutical co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "[t]he district court held claims 4 and 6 of the patent invalid because their specific activity of "at least about 160,000" was indefinite." After review, the CAFC states "[w]e therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase "at least about" indefinite where the metes and bounds of the term were not defined in the Specification.

Claim 54 is indefinite in the recitation "less than about" in lines 2-3 of the claim. The phrase "less than" typically indicates a maximum point; however, the phrase "less than" is controverted by the term "about," which implies that values above and below the indicated amount are permitted. Therefore, the juxtaposition of these two terms makes it unclear what maximum amount is encompassed by the claim.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 28-36, 38-44, 46-48, 50-52, and 54-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993).

Regarding claim 28, Anderson et al teach a method for synthesizing an oligonucleotide on a substrate. In a single exemplary embodiment, Anderson et al teach a first nucleotide capped with a trityl group attached to a cpg support (i.e., substrate; column 19, line 40-column 20, line 50). Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36)

forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Regarding claim 29, Anderson et al teach the method of claim 28, wherein a blocked nucleoside monomer is attached to the substrate by contacting the substrate with a fluid comprising a blocked nucleoside monomer at a location on the substrate that comprises hydroxy groups; namely, the blocked monomer in step ii of Table I is added to the unblocked attached nucleotide of step i, which has a free hydroxyl group at the 5' end generated by the detritylation step (column 19, line 40-column 20, line 50).

Regarding claim 30, Anderson et al teach the method of claim 28, wherein the steps are repeated a plurality of times (column 20, lines 2).

Regarding claims 31 and 34, Anderson et al teach the method of claim 28, wherein the substrate comprises a surface of a planar support; namely, the support is a flat disc (column 6, lines 49-56).

Regarding claim 32, Anderson et al teach the method of claim 28, wherein the displacing step causes minimal mixing of deblocking and purging fluids; namely, density differences are used to minimize mixing (column 10, lines 23-24).

Regarding claim 33, Anderson et al teach the method of claim 28, wherein the substrate comprises a surface of a support containable within a flow cell; namely, internal space for fluid flow so as to contact solid support (Column 5, lines 20-38).

Regarding claim 35, Anderson et al teach the method of claim 28, wherein the purging fluid has a density that is different from the deblocking fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D).

Regarding claims 36 and 38, Anderson et al teach the method of claim 28, wherein the deblocking fluid and the purging fluid have a density difference, expressed as the Atwood number, of at least about

0.01. In a single exemplary embodiment, Anderson et al teach the deblocking (detritylation) fluid has a density that is greater than that of methylene chloride (i.e., 1.325 g/mL; column 21, lines 1-10). Detritylation is followed with a wash using acetonitrile as a purging solution, which has a density of 0.714 g/mL (Table II, step 3). Calculating the density difference using pure methyl chloride results in an Atwood number of 0.2996; a higher density deblocking fluid gives a higher Atwood number.

Regarding claim 39, Anderson et al teach the method of claim 28, wherein the purging fluid is an organic fluid; namely, 50% dichloromethane and 50% dimethylformamide (Table II).

Regarding claim 40, Anderson et al teach the method of claim 28, wherein the purging fluid comprises an oxidizing agent; namely, the purging fluid is interpreted to be all of the fluids of Table I following the deprotection step i (column 20), which are introduced in one long series of changing densities (column 7, lines 5-19). The series that makes up the purging fluid includes the oxidizing agent iodine (step iv of Table I).

Regarding claims 41 and 42, Anderson et al teach the method of claim 28, wherein the purging fluid comprises a wash fluid; namely, step 3 of Table II is a washing step using 50% dichloromethane and 50% dimethylformamide (Table II).

Regarding claim 43, Anderson et al teach the method of claim 41, wherein the wash fluid is acetonitrile (column 13, line 67-column 14, line 1).

Regarding claim 44, Anderson et al teach the method of claim 28, wherein the deblocking fluid is displaced with a purging fluid in a manner that moves a stratified interface across the surface; namely, interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D).

Regarding claim 46, Anderson et al teach the method of claim 28, wherein the purging fluid limits the efficiency of the deblocking fluid; namely, the deblocking reaction requires acid (e.g., dichloroacetic acid; step i of Table I). Addition of any washing fluid decreases the concentration of acid, thereby limiting the efficiency of deblocking.

Regarding claim 47, Anderson et al teach the method of claim 29, wherein the hydroxyl groups are 5' OH groups of nucleoside polymers deblocked by the detritylation step (column 19, line 40-column 20, line 50).

Regarding claim 48, Anderson et al teach the method of claim 28, wherein the step of displacing occurs within a flow cell; namely, an internal space for fluid flow so as to contact a solid support (column 5, lines 20-38).

Regarding claim 50, Anderson et al teach the method of claim 28, wherein the blocking group is a trityl group (column 19, line 40-column 20, line 50), which is an acid sensitive group, and the deblocking fluid comprises dichloroacetic acid (step i of Table I).

Regarding claim 51, Anderson et al teach the method of claim 33, wherein the substrate is contained within a chamber of flow cell; namely, chamber 24 is which holds the particulate material (i.e., the substrate; figure 1 and column 11, line 24-column 12, lines 27). Chamber 24 is also connected to upper and lower fluid lines 100 and 102 (Figure 1), which are interpreted as fluid inlet and outlets.

Regarding claim 52, Anderson et al teach the method of claim 51, wherein the flow cell is oriented an at least partially vertical position; namely, the flow cell is attached to a rotor system, and is spun with the axis vertically (Abstract).

Regarding claim 54, Anderson et al teach the method of claim 28, wherein the deblocking fluid comprises an organic solvent; namely, acetonitrile (column 13, line 67-column 14, line 1). The vapor pressure of acetonitrile at 0°C and 1 ATM pressure is 24.75 mm Hg, which is 3.3 kPa.

Regarding claim 55, Anderson et al teach the method of claim 28, further comprising contacting the substrate comprising the attached blocked nucleoside polymer with an oxidation fluid prior to contacting with the deblocking fluid; namely., oxidation of an added nucleoside is performed before the sequential addition of the next monomer (Table I, step iv).

Regarding claim 56, Anderson et al teach a method for producing a substrate of at least two different oligonucleotides bonded to different locations on a surface of the substrate. In a single

exemplary embodiment, Anderson et al teach a substrate; namely, is a membrane incorporating interactive particles (column 6, lines 49-56), wherein the particles are the different locations of the surface of the membrane, which is the substrate. Anderson et al teach contacting tritylated nucleoside monomers with the supports, wherein terminal nucleotides on the supports have been previously detritylated to provide free 5'OH groups (column 19, line 40-column 20, line 50), wherein the 5' OH groups are the functional groups on the surface that bind the blocked (i.e., tritylated) monomers to the locations on the surface. Anderson et al also teach the newly attached nucleosides are subsequently detritylated (column 19, line 40-column 20, line 50), wherein the detritylation fluid is a deblocking fluid (Table I, step i, column 20). Anderson et al further teach washing the surface (Table I, column 20), wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). The washing solution is a purging solution that displaces the deblocking fluid from all of the locations. Anderson et al also teach reacting the newly unblocked monomers at the locations with another blocked nucleoside monomer; namely, the steps of the method are repeated on the substrate to attain the required chain length (column 20, line 2).

Regarding claim 57, Anderson et al teach the method of claim 56, wherein the at least two oligonucleotides comprise the same sequence; namely, the solutions are added to the support in a rotor (column 20, lines 55-65), which is interpreted as a single synthesis in a single rotor, producing one full length sequence at more than one location on the support.

Regarding claim 58, Anderson et al teach the method of claim 56, wherein the at least two oligonucleotides comprise different sequences; namely, at least one location has a failure sequence (column 20, lines 10-25), which is interpreted as a second different sequence in addition to the successfully synthesized sequences.

Regarding claim 59, Anderson et al teach the method of claim 56, further comprising contacting the substrate comprising the bonded blocked nucleoside polymer with an oxidation fluid prior to

contacting with the deblocking fluid; namely, oxidation of an added nucleoside is performed before the sequential addition of the next monomer (Table I, step iv).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 28 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Greene et al (*Protective Groups in Organic Synthesis*, 3rd ed., Wiley and Sons, New York, 1999, page 106).

Regarding claim 37, Anderson et al teach the method of claim 28 for synthesizing an oligonucleotide on a substrate. In a single exemplary embodiment, Anderson et al teach a first nucleotide capped with a trityl group attached to a cpg support (i.e., substrate; column 19, line 40-column 20, line 50). Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al

further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Anderson et al also teach the method of claim 28, wherein the deblocking fluid and the purging fluid have a density difference. Detritylation is followed with a wash using dichloromethane as a purging solution, which has a density of 1.325 g/mL (Table I, step i). Anderson et al also teach that a series of solutions (i.e., the deblocking fluid and purging fluid) is added in either increasing or decreasing density (column 20, lines 55-64).

Anderson et al do not explicitly teach the purging fluid density is higher than the deblocking fluid density.

However, Green et al teach the deblocking (i.e., cleavage) of dimethoxytrityl (i.e., trityl) groups of deoxyribonucleotides using 3% trichloroacetic acid (density 1.62 g/mL) in 95:5 nitromethane/methanol (densities 1.127 and 0.791 g/mL, respectively), with the added advantage that the mixture reduces the levels of depurination of the reaction product (page 106).

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). In the instant case, the solvent mixture is predominantly nitromethane, with a density of 1.127 g/mL, with 5% methanol, having a lower density. A final concentration of 3% of the higher density trichloroacetic acid is believed to produce a solution with an overall density nearly equal to that of nitro methane, because similar

percentages of both a higher density liquid and a lower density liquid are added. Thus, the final density of the solution of Greene et al is believed to be lower that 1.325 g/mL, which is the density of the purging fluid of Anderson et al.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the method as taught by Anderson et al with a deblocking solution of lower density as taught by Greene et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a reduction of the levels of depurination of the reaction product as explicitly taught by Greene et al (page 106).

9. Claims 28 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Mian et al (U.S. Patent No. 6,319,469, issued 20 November 2001).

Regarding claim 45, Anderson et al teach the method of claim 28 for synthesizing an oligonucleotide on a substrate. In a single exemplary embodiment, Anderson et al teach a first nucleotide capped with a trityl group attached to a cpg support (i.e., substrate; column 19, line 40-column 20, line 50). Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Anderson et al also teach the method of claim 44, wherein the deblocking fluid is displaced with a purging fluid in a manner that moves a stratified interface across the surface; namely, interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D).

While Anderson et al are silent with respect to specific flow rates, Anderson et al do teach the method wherein the flow rate is controlled and monitored during passage of reagents (column 5,lines 25-27 and column 14, lines 44-53 21). Anderson et al further teach that it is advantageous to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (column 21, lines 30-65). Thus, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step.

In addition, Mian et al teach a method of synthesizing oligonucleotides on a disc (Figure 23b and column 5, lines 65-67), wherein the flow rates are from about 1 cm/sec to about 20 cm/sec having the added advantage that variable flow rates within the claimed range allow fluid transfer over a wide range of times scales as required by the various processes (column 12, lines 40-57).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the flow rates of the method of Anderson et al to with range of flow rates as taught by Mian et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in flow rates that allow fluid transfer over a wide range of times scales as required by the various processes as explicitly taught by Mian et al (column 12, lines 40-57).

10. Claims 28-29 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Gamble et al (U.S. Patent No. 5,874,554, issued 23 February 1999).

Regarding claim 49, Anderson et al teach the method of claim 28 for synthesizing an oligonucleotide on a substrate. In a single exemplary embodiment, Anderson et al teach a first nucleotide capped with a trityl group attached to a cpg support (i.e., substrate; column 19, line 40-column 20, line 50). Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Anderson et al also teach the method of claim 29, wherein a blocked nucleoside monomer is attached to the substrate by contacting the substrate with a fluid comprising a blocked nucleoside monomer at a location on the substrate that comprises hydroxy groups; namely, the blocked monomer in step ii of Table I is added to the unblocked attached nucleotide of step i, which has a free hydroxyl group at the 5′ end generated by the detritylation step (column 19, line 40-column 20, line 50).

Anderson et al does not teach deposition by pulse-jetting.

However, Gamble et al teach a method of synthesizing oligonucleotides by pulse jetting monomers (Abstract, line 1) with the added benefit that pulse jetting reduces reagent waste (column 1, lines 50-55).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Anderson et al with the pulse jetting of monomers as taught by Gamble et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in reducing reagent waste as explicitly taught by Gamble et al (column 1, lines 50-55).

11. Claims 28, 44 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Farr (U.S. Patent No. 3,969,250, issued 13 July 1976).

Regarding claim 53, Anderson et al teach the method of claim 28 for synthesizing an oligonucleotide on a substrate. In a single exemplary embodiment, Anderson et al teach a first nucleotide capped with a trityl group attached to a cpg support (i.e., substrate; column 19, line 40-column 20, line 50). Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Anderson et al also teach the method of claim 44, wherein the deblocking fluid is displaced with a purging fluid in a manner that moves a stratified interface across the surface; namely, interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D).

Anderson et al does not teach a pressure gradient.

However, Farr teaches stratification of liquids using a pressure gradient; namely, creation of supernatant fluid by centrifuging immiscible liquids (column 1, lines 5-10) with the added advantage that the stratification (i.e., the creation of a supernatant) eliminates the need for decanting, thereby minimizing labor and possible contamination of the sample (column 2, lines 24-26).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified the method comprising a stratified interface as taught by Anderson et al by using a pressure gradient as taught by Farr with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in minimizing labor and possible contamination of the sample as explicitly taught by Farr (column 2, lines 24-26).

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Applicant is advised that should claim 31 be found allowable, claim 34 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

14. Claims 28-60 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7-36, and 41 of copending Application No. 11/234,701 in view of Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993). Both sets of claims are drawn to methods of synthesis comprising attached blocked nucleosides, deblocking fluids, purging fluids, attaching another blocked monomer, repetition of steps, planar supports, flow cells, and density differences. The instant claims are drawn to synthesis of an oligonucleotide, defined in the instant specification as being a single stranded multimer from about 10 to 100 nucleotides and up to 200 nucleotides in length. The claims of the '701 application are drawn to synthesis of a nucleic acid, which can be interpreted as the genus of the instantly claimed species.

Anderson et al teach the use of oligonucleotides approximately 15-18 or more nucleotides long, wherein the oligonucleotides have the added advantage of achieving specificity in intracellular hybridization (column 2, lines 40-50).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as claimed in the '701 application to synthesize oligonucleotides as taught by Anderson et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in nucleic acids that achieve specificity in intracellular hybridization as explicitly taught by Anderson et al(column 2, lines 40-50).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 56-59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, and 12-14 of copending Application No. 10/813,337 in view of Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993). Both sets of claims are drawn to methods comprising contacting blocked monomers at least two locations, removing blocked groups,

reiterating steps, oxidizing fluids, a plurality of fluids, flow cells, and pulse jets. The claims of the '337 application do not recite displacing the blocking fluid with a purging fluid or a triple phase interface.

However, Anderson et al teach a method for synthesizing an oligonucleotide on a substrate, comprising a first nucleotide capped with a trityl group attached to a cpg support (i.e., substrate; column 19, line 40-column 20, line 50). Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the method provides the advantage of allowing precise control of fluid flow and minimization of micro- and macro-anomalous flow (column 5, lines 30-35).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as claimed in the '337 application with the fluid displacement as taught by Anderson et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing precise control of fluid flow and minimization of micro- and macro-anomalous flow as explicitly taught by Anderson et al (column 5, lines 30-35).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 28, 30, 32-33, 35-36, and 38-48 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, and 7-16 of copending Application No. 10/813,331 in view of Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993). Both sets of claims are drawn to methods comprising nucleoside monomers, deblocking, density

differences, flow cells, flow rates, and pulse jets. While the instant claims only teach two liquids, the open language "comprising" in the instant claims encompasses the additional limitations of a oxidizing fluid in the '331 claims. The claims of the '331 application do not recite displacing the blocking fluid with a purging fluid.

However, Anderson et al teach a method for synthesizing an oligonucleotide on a substrate, comprising a first nucleotide capped with a trityl group attached to a cpg support (i.e., substrate; column 19, line 40-column 20, line 50). Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the method provides the advantage of allowing precise control of fluid flow and minimization of micro- and macro-anomalous flow (column 5, lines 30-35).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as claimed in the '331 application with the fluid displacement as taught by Anderson et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing precise control of fluid flow and minimization of micro- and macro-anomalous flow as explicitly taught by Anderson et al (column 5, lines 30-35).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 28-59 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4-5 of copending Application No. 10/449,838 in view

of Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993). Both sets of claims are drawn to methods comprising contacting a ligand array with a feature modification reagent (e.g., contacting the monomer array of the instant claims with a fluid that changes the surface [i.e., by oxidizing the monomers]). While the instant claims do not teach high surface tension deposition fluids, the open language "comprising" in the instant claims encompasses the additional limitations. The claims of the '838 application do not recite displacing the blocking fluid with a purging fluid.

However, Anderson et al teach a method for synthesizing an oligonucleotide on a substrate, comprising a first nucleotide capped with a trityl group attached to a cpg support (i.e., substrate; column 19, line 40-column 20, line 50). Anderson et al further teach detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al further teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the method provides the advantage of allowing precise control of fluid flow and minimization of micro- and macro-anomalous flow (column 5, lines 30-35).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as claimed in the '838 application with the fluid displacement as taught by Anderson et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing precise control of fluid flow and minimization of micro- and macro-anomalous flow as explicitly taught by Anderson et al (column 5, lines 30-35).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

18. Pages 9-14 of Applicant's arguments filed 25 September 2006 (i.e., the "Remarks") with respect to the rejection(s) of the claim(s) under Gao et al have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the teachings of Anderson et al as outlined above.

19. Applicant's arguments on page 14 of the Remarks with respect to the statutory double patenting rejection(s) of claim(s) 28-59 under have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new rejection is made on the ground of nonstatutory obviousness-type double patenting.

20. Applicant's arguments on pages 15-17 of the Remarks with respect to the nonstatutory double patenting rejection(s) of the claim(s) over the '006, '337, '331, and '838 applications have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new rejection is made on the ground of nonstatutory obviousness-type double patenting in view of Anderson et al.

Conclusion

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Examiner
Art Unit 1634

JULIET C. SWITZER
PRIMARY EXAMINER